IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Gonda et al.
Serial No.	:	09/848,774
Filed	:	May 3, 2001
For	:	A METHOD OF TREATING DIABETES MELLITUS IN A PATIENT
Examiner	:	Aaron J. Lewis
Group Art Unit	:	3761

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I hereby certify that the attached correspondence comprising:

1. Reply Brief (14 pages)

is being deposited with the United States Patent and Trademark Office **via facsimile no. 571-273-8300 on February 28, 2006.**

Rashida Haji
(name of person mailing paper)

Rashida Haji
(signature of person mailing paper)

Attorney Docket No.: 6809.220-US Patent

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REPLY BRIEF

Sir:

Appellants hereby reply to the Examiner's Supplement/Second Answer, pursuant to 37 C.F.R. § 1.193, in their appeal of the final rejection of the claims presently pending in the above-referenced application. This Reply Brief is being submitted as of right within two months of the date of the Examiner's Answer, which was mailed in error to the previous attorney of record in the application.

Applicants are filing as their reply the same reply brief that they filed in response to the Examiner's first answer and respectfully request that this appeal be docketed as quickly as possible as the appeal has now been pending for several years. Indeed, applicants first filed a reply to the Examiner's answer in October 2004.

The PTO is hereby authorized to charge any necessary payments, or credit any overpayments, to Deposit Account No. 14-1447.

I. NATURE AND STAGE OF THE APPEAL

This is an appeal from the decision of the Primary Examiner in an Office Action dated April 15, 2003, finally rejecting claims 22-38, all of the claims of the above-referenced application, and the Advisory Action dated July 3, 2003, denying Appellants' request for reconsideration.

Claims 22-38 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Schenk, WO 90/07351 in view of Velasquez, U.S. Patent No. 5,192,548.

The Application was amended concurrently with the filing of the present appeal. Now claims 22, 23, 25, 26, 31 and 35 remain pending in the application, as amended.

Appellants filed a Notice of Appeal on October 10, 2003, with the corresponding fee, and an Appeal Brief, fee, and Amendment on May 10, 2004.

An Examiner's Answer was mailed on August 12, 2004, to an incorrect address.

II. SUMMARY

A. The Claimed Invention

The claimed invention relates to the delivery of a controlled dose of insulin to the *bloodstream* of a patient *via inhalation*. The invention is not directed merely to the delivery of a medicament to a patient's lungs, as the rejection of the claims and the Examiner's Answer both, in effect, suppose.

The claims require not only this key feature, but also call out additional limitations:

- claim 23 requires for each treatment that the dose delivered to the blood remains relatively constant;
- claim 25 requires a controlled dose sufficient to achieve satisfactory blood glucose control;
- claim 31 requires absorption of 1-50 units of insulin; and
- claim 35 requires the dose absorbed into the blood be controlled and repeatable.

B. Appeal Brief

Appellants' Appeal Brief described in detail how:

- the rejection of the claims failed to establish a *prima facie* case of unpatentability;
- the applied references fail to teach or suggest the invention as a whole, which includes *controlled delivery of insulin to the bloodstream* of a patient *through inhalation,* as well as other limitations; indeed the references neither recognize the problems associated with this delivery, which is critical for the treatment of diabetes with insulin, nor even begin to provide a solution;
- in an attempt to supply disclosure missing from the applied references the PTO erred as a matter of law in applying an "obvious to try" standard; and
- the PTO's rejection of the pending claims also relies impermissibly on an "implicit" or inherent obviousness standard.

C. Examiner's Answer

The Examiner's Answer does not address or overcome Appellants' arguments and overlooks many of them. In the Examiner's Answer the PTO:

- fails to show that the cited references, whether alone or in combination, recognized or disclosed getting medicament into the *bloodstream* of a patient *through inhalation*, much less getting into the bloodstream a *controlled dose* of insulin necessary for the safe treatment of diabetes, and explicity required by the pending claims;
- acknowledges the deficiencies of the rejection by attempting to include a third reference into the combination of references relied upon in support of the rejections: Harrison's Principles of Internal Medicine, which was discussed by

Appellants in the pending application at para. 00235, and which does not relate to delivery of insulin through inhalation;

- contends that "one of ordinary skill would also recognize that [Schenk] as modified by [Velasquez] must be administered to patients under known guidelines of standard medical practice in the treatment of diabetes mellitus" – despite that there were *no such guidelines* for treatment of diabetes through administration of powdered insulin to the bloodstream via inhalation prior to the claimed invention;

- asserts, without factual basis and contrary to the teachings of the involved application, that any delivery of insulin using an inhaler would "necessarily result in and would be exemplary of a treatment for diabetes" (Answer at 6);

- incorrectly contends that insulin "is a prescription medicine" and that one of ordinary skill is therefore a physician (Answer, bridging pp.6-7);

- admits the prior art combination does not expressly disclose any amounts of insulin being delivered to the bloodstream;

- argues, again without any factual basis, that in the course of treatment of diabetes through insulin inhalation "one of ordinary skill being equipped with known medical guidelines for treatment of diabetes mellitus would know to make adjustments in the quantity of powdered medicament in order to provide a dose which would effectively bring a patient's blood glucose within a 'normal' range";

- fails to identify any legal authority in support of its persistent reliance on the legally erroneous "obvious to try" standard, ignoring the claimed subject matter as a whole and, without any factual support whatsoever, arguing that the recited controlled dose "can be arrived at through mere routine obvious experimentation" (Answer at 7), when the references do not even suggest or hint that it is possible to deliver a controlled dose into the bloodstream via inhalation of powdered insulin;

- similarly, fails to identify any legal authority in support of its legally erroneous use of an implicit or inherent obviousness standard and argues, without any factual basis and contrary to the teachings of the involved application, that any inhalation of insulin would "necessarily result in and would be exemplary of a treatment for diabetes" (Answer at 7), when none of the applied references so much as hints at a treatment for diabetes that comprises delivery into the bloodstream of a controlled dose of insulin via the lungs; and

- raises apparently new grounds in support of the rejection, without designating them as such under 37 C.F.R. §§ 41.39(a)(2), (b), in particular: (1) adding

Harrison to the combination of Schenk and Velasquez; (2) alleging that specific values and ranges recited in the pending claims are not critical; and (3) alleging that Laube, which relates to liquid aerosolization, has a direct and relevant bearing on powdered insulin inhalation (Answer at pp. 7-8).

III. REPLY

A. The Examiner's Answer Reflects a Continuing Misapprehension of the Applied References

The PTO has misread and incorrectly applied the references against the pending claims. None of the three references now relied on in rejecting the claims (Schenk, Velasquez or Harrison), whether alone or in combination, discloses or suggests delivery of anything to the *bloodstream* of a patient through inhalation, let alone a controlled dose of insulin.

Schenk merely discloses an inhaler. At most this would suggest delivery of a substance to the *lungs* of a patient. Schenk has nothing to do with delivery to a patient's *bloodstream* of a controlled dose of medication and does not recognize or mention a need to maintain any level of delivery of a drug to the *bloodstream* of a patient, much less a controlled delivery of specific quantities.

Disclosing only that a blister pack can contain insulin, Velasquez, too, lacks any disclosure of delivery of anything, and certainly discloses nothing about delivery of a medicament *via the lungs* and into the *bloodstream* in a precisely controlled manner. In fact, Velasquez makes only passing reference to insulin as only one in a long list of forty or so other medications that can be supplied in a powdered form and does not suggest anything about how they may be administered via an inhaler to achieve a controlled bloodstream dose.

Harrison, identified by Appellants in their application and now for the first time relied on by the PTO in the Examiner's Answer, has nothing to do with inhalation of insulin and is without relevance to the pending claims. Harrison relates only to conventional subcutaneous injection of insulin and does not teach anything with respect to absorption of inhaled powdered insulin.

There is absolutely no teaching in the cited references that inhaled, powdered insulin could be used safely and effectively to treat diabetes. Similarly, the references provide no teaching that an inhaler could be used in delivering controlled doses of a powdered medicament to the bloodstream of a patient. Still further, the references fail to teach that, by inhaling powdered insulin, one could get a controlled dose into the *bloodstream* with the precision necessary to treat diabetes. The applied references completely fail to disclose how one would be able to use an insulin inhaler to do so, much less to deliver certain quantities to the lungs and, by virtue of this delivery, controlled quantities to the bloodstream.

In the absence of any suggestion in the prior art of the claimed subject matter as a whole, the PTO's rejection has relied on the knowledge of Applicants' invention to pick and choose among the cited disclosures, and even to find disclosures in the art where none is actually present, in order to deprecate the claimed invention.

These shortcomings are fatal to the rejection. They cannot be, and are not, overcome by the PTO's vague, factually unsupportable, and legally erroneous "obvious to try"/routine experimentation and "implicit obviousness" arguments.

B. PTO Erroneously Relies on Non-Existent "Known Guidelines"

In an attempt to plug the gaps in the applied references, the PTO alludes to "known guidelines." (Answer at 6). But the PTO has not identified *any* guidelines for the delivery of

powdered insulin to the *bloodstream* of a patient through *inhalation*. To the extent the "known guidelines" are intended to refer to the Harrison reference, those contemplate delivery through *injection*, not *inhalation*. If anything, Harrison teaches away from inhalation by focusing specifically on injection as necessary for the type of control necessary for effective and safe treatment of diabetes.

C. No Legal Authority Supports the PTO's Actual Use of "Obvious to Try" and "Implicit" or Inherent Obviousness Standards

In their Appeal Brief, Appellants explained in detail and with citation to appropriate legal authority how the PTO, in lodging the present rejections, applied erroneous legal standards. In an attempt to supply the acknowledged deficiencies in the applied references, the PTO applied (1) an impermissible "obvious to try" legal standard when relying on "mere routine obvious experimentation and observation", and (2) an equally inappropriate "implicit" or inherent obviousness standard with respect to any inhalation of insulin "necessarily" resulting in a controlled delivery of insulin to the bloodstream for purposes of treating for diabetes.

The PTO has not addressed these legal issues, as it is required to do by MPEP § 1208.

Though it now contends that "[t]he propriety of the prior art combination is not based upon an 'obvious to try' motivation...," this is not what Appellant argued. That combination, even if made, does not show controlled delivery of insulin via inhalation to the bloodstream of a patient. What Appellant argued was that the PTO's contention that "the amount of insulin employed and the amount of insulin being absorbed...can be arrived at through mere routine obvious experimentation and observation" represents a legally prohibited "obvious to try" standard of Patentability. (Appeal Brief at 11). Indeed, there can be no other way to view the

PTO's rejection given that the references (1) fail to offer any hint or suggestion that one could treat diabetes through inhalation of powdered insulin and (ii) fail to show that inhalation of powdered insulin would result in absorption of a controlled dose into the bloodstream. The references offer no suggestion of a quantity of insulin, a relationship between inhaled insulin and absorbed insulin, or a method for achieving a controlled dose of insulin to the bloodstream based on inhalation of insulin in powdered form.

The PTO has ignored this argument and its supporting legal authority, in disregard of MPEP § 1208, and has persisted with arguments of the following sort: "[o]ne of ordinary skill being equipped with known medical guidelines for treatment of diabetes mellitus would know to make adjustments in the quantity of powdered medicament in order to provide a dose which would effectively bring a patient's blood glucose within a 'normal' range." (Answer at 7). Yet the PTO remains silent as to *how* one would "know to make adjustments" through inhalation without the benefit of the present application, and *how* one would go about making the "adjustments" even if it had been known they could be made. The PTO does not state what in the references would motivate one even to attempt to treat diabetes by inhaling powered insulin. That powdered insulin could be inhaled would, at best, be a suggestion to try, which the Appeal Brief made clear is an impermissible standard for rejection of patent claims.

Also in disregard of MPEP § 1208, the PTO has overlooked Appellants' argument that the PTO's reliance on an implicit or inherent obviousness standard constitutes legal error.

D. The Examiner's Answer is Based, in Part, on Misstatements of Fact

The PTO has asserted without any factual basis, and contrary to the teachings of the involved application, that any delivery of insulin using an inhaler would "necessarily result in

and would be exemplary of a treatment for diabetes." (Answer at 6). This contention is gravely mistaken. If followed, it could lead either to harmfully ineffective diabetes treatment or to the injury and possible death of the diabetic patient.

Similarly, the PTO contends that insulin "is a prescription medicine" and that one of ordinary skill is therefore a physician. (Answer, bridging pp. 6-7). This, too, is incorrect. Insulin does not generally require a prescription in the U.S.

E. New Grounds of Rejection

New grounds for rejection may not be raised in an Examiner's Answer. 37 C.F.R. § 1.193(a)(2); MPEP § 1208.01. The Examiner's Answer nevertheless contains several apparent new grounds of rejection.

The Examiner's Answer, for the first time, relies on the following reasoning:

i. "one of ordinary skill would also recognize that any powdered insulin administered using the inhaler of Schenk et al as modified by Velasquez et al. must be administered to patients under *known guidelines of standard medical practice* in the treatment of diabetes mellitus." (Examiner's Answer at 6, emphasis added);

ii. "review of the instant specification reveals no criticality for a dose of insulin being 1-50 units" (Examiner's Answer at 7);

iii. "review of the instant specification reveals no criticality for the amount of insulin in the aerosolized suspension being 2-10 time higher than the amount needed to be absorbed into a patient's bloodstream" (Examiner's Answer at 8);

iv. "it is submitted that the amount of any aerosolized medicament in any inhaler would need to exceed that which is intended to be absorbed into a patient's blood stream due to losses of medicament" (Examiner's Answer at 7, citing Laube).

None of these new grounds of rejection were necessitated by the Appeal Brief and each of them is without merit. Appellants respectfully request that they be withdrawn.

IV. CONCLUSION

As is described in detail above, the Examiner's Answer fails to adequately address, or in several instances address at all, the points raised in Appellants' Brief. In particular, there are three references now apparently relied upon by the Examiner. All three when read together fail to teach that a controlled dose of insulin can be delivered to the patient's bloodstream via inhalation of a powdered insulin. Even assuming, without conceding, that Schenk and Velasquez could be understood to suggest inhalation of powdered insulin, they still would not suggest that it is possible to get absorption of the controlled quantities of insulin into the bloodstream necessary to control blood glucose levels in a diabetic patient. Harrison merely discloses treatment of diabetes to achieve normal blood glucose levels through subcutaneous injection, but has nothing to do with inhalation of insulin.

In addition to the above flaws, the rejection and the Examiner's Answer rely on erroneous legal standards, misstatements of fact, and impermissible newly-raised grounds of rejection. In view of the many errors and omissions in the Examiner's Answer, and for the reasons set forth above, Appellants respectfully submit that, claims 22, 23, 25, 26, 31 and 35 were improperly rejected as unpatentably obvious and are allowable over the cited art. The PTO has erred. Applicants request reversal of the rejection.

Respectfully submitted,

Date: February 28, 2006

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APPENDIX OF CLAIMS

22. A method for treating diabetes mellitus in a patient comprising the steps of:

a. supplying a predetermined amount of dry insulin powder to an inhalation device;

b. releasing a pressurized gas over the predetermined amount of dry insulin powder to create an aerosolized suspension comprising powder suspended in air, wherein the aerosolized suspension contains an amount of insulin that is 2-10 times higher than the amount needed to be absorbed in the bloodstream of the patient; and

c. inhaling the aerosolized suspension at a flow rate and volume sufficient to allow the patient to absorb in the bloodstream a controlled dose of insulin that comprises between 1-50 units of insulin.

23. The method of claim 22, wherein steps a-c may be repeated periodically as needed to treat the patient and wherein the amount of insulin supplied to the bloodstream in step c remains relatively constant for each repetition of steps a-c.

25. A repeatable method of regulating blood glucose levels in a human patient, the method comprising the steps of:

a. supplying a fixed quantity of dry insulin powder to a portion of a hand held inhalation delivery device;

b. propelling a gas over the fixed quantity of dry powder to produce, in a repeatable manner, an aerosolized suspension of insulin, the aerosolized suspension containing more insulin than is required in the bloodstream of the patient to achieve a satisfactory blood glucose level; and

c. flowing at least a portion of the aerosolized suspension through a mouth piece on the device and into the lungs of the patient in a manner sufficient to cause the patient to absorb in the patient's bloodstream a sufficient, controlled quantity of insulin to achieve acceptable blood glucose level following treatment.

26. The method of claim 25, wherein steps a-c may be repeated periodically as needed to treat the patient and wherein the amount of insulin supplied to the bloodstream in step c remains relatively constant for each repetition of steps a-c.

31. A repeatable method of lowering a patient's serum glucose level to acceptable value, the method comprising the steps of:

a. supplying a predetermined amount of dry insulin powder to a medical device;

b. releasing a compressed gas over the dry insulin powder to form a suspension comprised of dry insulin powder and air; and

c. inhaling at least a portion of the suspension at a flow rate and volume sufficient to deposit a sufficient, controlled quantity of insulin in the patient's lungs so that the patient absorbs into the blood between 1 and 50 units of insulin, thereby lowering the patient's blood glucose level to an acceptable value between 50 mg/dl and 300mg/dl.

35. (Amended) A method of administering insulin to a diabetic patient to control serum glucose levels via a hand held inhalation device, the method comprising the steps of:

a. supplying a predetermined quantity of insulin powder to a portion of the device;

b. aerosolizing the insulin powder to form a cloud of insulin within the device, the cloud comprised of air and suspended insulin particles, the quantity of insulin particles being 2-10 times the dosage of insulin required to be delivered into the patient's blood to achieve acceptable blood glucose level;

c. administering to the patient's bloodstream via the patient's lungs a sufficient controlled and repeatable quantity of insulin from the cloud to produce an acceptable blood glucose level in the patient.